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A double-blind randomized study of aminoglycoside infusion with combined therapy for pulmonary *Mycobacterium avium* complex disease

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Summary A prospective study of the clinical efficacy of an aminoglycoside antibiotic (streptomycin, SM) for the treatment of pulmonary *Mycobacterium avium* complex (MAC) disease was carried out. In a multicenter trial, patients with pulmonary MAC disease received protocol-guided combined chemotherapy with or without SM. SM was given to the patients intramuscularly 15 mg/kg three times per week for the initial 3 months and three other antibiotics (rifampicin, ethambutol, and clarithromycin) were added and administered for over 24 months after the conversion of MAC strains. From April 1998 to December 2004, 160 HIV-negative patients were enrolled in this trial. Fourteen patients were found to be ineligible because they could not continue the treatment, and they were excluded from the analysis after randomization. Seventy-three patients were assigned to receive combined chemotherapy with SM (group A) and 73 were assigned to receive combined chemotherapy without SM (group B). The median durations of treatment were 27.6 months in group A and 28.4 months in group B. The difference in the backgrounds of the groups was not statistically significant. There were no differences in microbiological and radiological findings between the groups, but the sputum conversion rate for pulmonary MAC disease at the completion of treatment was significantly higher in group A than that in group B. Although, there were no significant differences in the sputum relapse rate and clinical improvement including both clinical symptoms and radiological findings, group A showed better initial microbiological response than group B. As for adverse reactions and abnormal laboratory findings, there were no significant differences between the groups.

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Based on the results of this double-blind randomized study, we support treatment including SM according to both the American Thoracic Society (ATS) and the Japanese Society for Tuberculosis (JST) guidelines for patients with pulmonary MAC disease without HIV infection.

Introduction

Pulmonary *Mycobacterium avium* complex (MAC) disease is the most common nontuberculous mycobacterial infectious disease in Japan and is increasing in incidence.[1] Regarding its treatment, Wallace et al. initiated a clinical trial of regimens including rifabutin (RBT) or rifampicin (RFP), ethambutol (EB), clarithromycin (CAM), and initial streptomycin (SM), and reported that this regimen achieved satisfactory results.[2] In 1997, the American Thoracic Society (ATS) recommended a four-drug regimen including CAM or azithromycin (AZM), RFP or RBT, EB, and an initial aminoglycoside (streptomycin) for pulmonary MAC disease.[3] Thereafter, in 1998, the Japanese Society for Tuberculosis (JST) also recommended a four-drug regimen including CAM, RFP, EB, and an initial aminoglycoside.[4] Recently, although there have been several reports on combined therapy including an aminoglycoside (SM or kanamycin (KM)), there are no data comparing CAM containing regimens with and without an aminoglycoside antibiotic. Therefore, we prospectively investigated randomized trials of the conversion of MAC strains in two groups treated with and without SM for over 24 months to investigate the clinical efficacy of this aminoglycoside for pulmonary MAC disease.

Patients and methods

Patients

From April 1998 to December 2004, 160 eligible patients were enrolled in this randomized, double-blind, placebo-controlled trial, which was conducted at Kawasaki Medical School Hospital and ten hospitals belonging to the Research Committee of *Mycobacterium* in the Chugoku and Shikoku areas. A regional institutional review board approved the protocol, and written informed consent was obtained from all participants or their authorized representatives.

Selection criteria

Selection for this study required that patients satisfy the ATS diagnostic criteria for nontuberculous mycobacterial infection,[3] and that they have negative serological findings for HIV or the absence of obvious risk factors for that disease were required.

The inclusion criteria for this trial were positive sputum cultures for MAC at entry into the study, and availability for an interval of treatment of over 24 months after the conversion of MAC strains. Fourteen patients who could not undergo treatment for over 24 months after the conversion of MAC strains were excluded. The clinical features of the 146 remaining patients were age, gender, smoking and alcoholic history, underlying diseases involving corticosteroid administration, clinical symptoms (continuous cough, weight loss ($\geqslant$5 kg during 3 months), hemosputum or hemoptysis, and fever), microbiological findings, radiological findings, clinical efficacy, and adverse reactions including abnormal laboratory findings.

Treatment assignments (Table 1)

Patients were randomly assigned in a 1:1 manner to receive a streptomycin intramuscular injection with other antituberculous drugs (group A) or only the other antituberculous drugs (group B) at each hospital. Randomization schemes were generated in blocks of 11 for each participating site by a central randomization center. The randomization assignments were sent to the recruiting center in sealed envelopes. The patients and the investigators were blinded to the patients' treatment assignments. SM was given to group A intramuscularly 15 mg/kg (500–1000 mg) with 10% NaCl (natrium sodium) 1 ml three times per week for the initial 3 months along with RFP 10 mg/kg/day (350–650 mg), EB 15 mg/kg/day (500–1000 mg), and CAM 15 mg/kg/day (500–1000 mg), whereas group B was given only 10% NaCl 1 ml intramuscularly (placebo control) without SM, but with RFP 10 mg/kg/day (350–650 mg), EB 15 mg/kg/day (500–1000 mg), and CAM 15 mg/kg/day (500–1000 mg). The overall treatment period was over 24 months after the conversion of MAC strains for patients who routinely showed severe adverse reactions.

Table 1 Randomized treatment regimen for pulmonary MAC disease (146 cases).

(A) RFP 10 mg/kg/day+EB 15 mg/kg/day+CAM 15 mg/kg/day+10%NaCl 1 ml with SM 15 mg/kg/3 times/week (73 cases)
(B) RFP 10 mg/kg/day+EB 15 mg/kg/day+CAM 15 mg/kg/day+10%NaCl 1 ml without SM (placebo)/3 times/week (73 cases)

RFP: rifampicin, EB: ethambutol, CAM: clarithromycin, SM: streptomycin NaCl: Natrium sodium.

Microbiological examination

Routine expectorated sputum was submitted for examination by Ziehl–Neelsen staining on three consecutive days at entry into the randomized trial. Specimens submitted for culture were digested and decontaminated by the sodium hydroxide method, and the samples were identified and differentiated by growth characteristics and conventional biochemical tests. *Mycobacterium avium* and *Mycobacterium intracellulare* were identified by the Amplicor polymerase reaction (PCR) assay (Roche Diagnostic Systems, Inc., Branchburg, NJ). Patients were examined every 2 weeks for the first 3 months, every 4 weeks thereafter during the therapy, and at least every 2 months during the follow-up after the completion of the therapy. Sputum was submitted for examination at every visit.

Radiological and laboratory examination

Computed tomography (CT) was performed initially in all patients and every 3 months thereafter to evaluate lesions, including cavities and bronchiectasis, and underlying pulmonary conditions. A chest roentogenograph was taken initially and every month thereafter. Extension of lesions was evaluated on the basis of both chest roentogenographs and chest CT findings. A peripheral blood cell count was performed and aminotransferase, total bilirubin and serum creatinine were measured at each visit during the therapy. Patients were advised to consult an otolaryngologist and an ophthalmologist initially, and as needed thereafter. A visual activity test, perimetry, and a red–green color discrimination test were routinely performed every month to check for EB toxicity.

Assessment of microbiological efficacy

Sputum conversion was defined as three consecutive negative sputum cultures within 6 months, with the time of conversion defined as the date of the first negative culture. If the patient could not expectorate sputum during the treatment duration, the sputum was considered to have converted to negative. The sputum relapse rate was defined as two consecutive positive cultures after sputum conversion.

Assessment of clinical efficacy

Clinical efficacy was evaluated on the basis of clinical improvement including both clinical symptoms (ones which were considered comparatively characteristic for active pulmonary MAC disease such as continuous cough, weight loss ($\geqslant$5 kg during 3 months), hemosputum or hemoptysis, fever) and radiological findings, and the opinions of several attending respiratory specialists were inserted. The treatment regimen of each patient was blinded for these attending respiratory specialists. Clinical improvement was defined as follows: (1) ''improving'' if both abnormal shadows had decreased within half of the lesion before treatment and clinical improvement of any clinical symptoms was found; namely, a decrease in continuous cough, normalization of weight loss or body temperature, or diminishment of hemoptysis or hemosputum, (2) ''worsening'' if both abnormal shadows had increased compared with the lesion before treatment and any clinical symptoms had increased, and (3) ''unchanging'' consisted of all patients except the patients who clinical efficacy was defined ''improving'' and ''worsening''.

Drug susceptibility

The MAC isolates obtained at entry were stored in an 85% 7H9 medium: 15% glycerol at $-80\,^{\circ}C$. Minimal inhibitory concentrations (MICs) to SM were determined by microdilution using twofold drug dilutions in Middlebrook 7H9 broth (pH corrected to 7.4) or dextrose (OAD), as previously described.[5] Isolates were interpreted as SM-susceptible if they had MICs of 2 μg/ml or less and resistant if they had MICs of $>4\,\mu$g/ml. Values of 2–4 μg/ml were considered intermediate.

Statistical analysis

Data were analyzed using standard methods. In all cases, statistical significance was defined as a two-tailed test with an α of 0.05. All statistical calculations were performed using the SAS System for Windows (release 9.0; SAS Institute, Cary, NC). Additional information on the sequential design and all analyses is available in the online supplement.

Results

Background

From April 1998 to December 2004, 160 HIV-negative patients were newly diagnosed with pulmonary MAC disease at 11 hospitals. None of them were previously treated with macrolide antibiotics (CAM or AZM) for pulmonary MAC disease and no in vitro susceptibility studies for antituberculous drugs including macrolide antibiotics were previously done on any of the MAC isolates from any of these patients. Among the 160 patients, 14 patients were considered ineligible because of difficulty in visiting the hospital regularly (geographic distance). However, the remaining 146 patients (71%) fulfilled the eligibility criteria and were enrolled in this protocol. They were randomly divided into patients receiving SM (73 patients, group A) and not receiving SM (73 patients, group B) (Fig. 1). Table 2 lists the backgrounds of the two groups. No significant differences were found in age, gender, smoking habits, chronic alcoholism, underlying diseases (group A and group B, respectively): respiratory diseases (27 versus 29), non-respiratory diseases (16 versus 18), and corticosteroid administration (3 versus 4). Antituberculous drugs were administered before admission (16 versus 14). SM was administered to 3 patients in group A and 3 patients in group B for treatment of pulmonary tuberculosis. Table 3 shows the clinical, microbiological and radiological findings at study entry. No significant differences were noted in clinical symptoms, identified pathogens and extension, location, and characteristics of the lesions on radiological findings such as bronchiectasis and cavity.

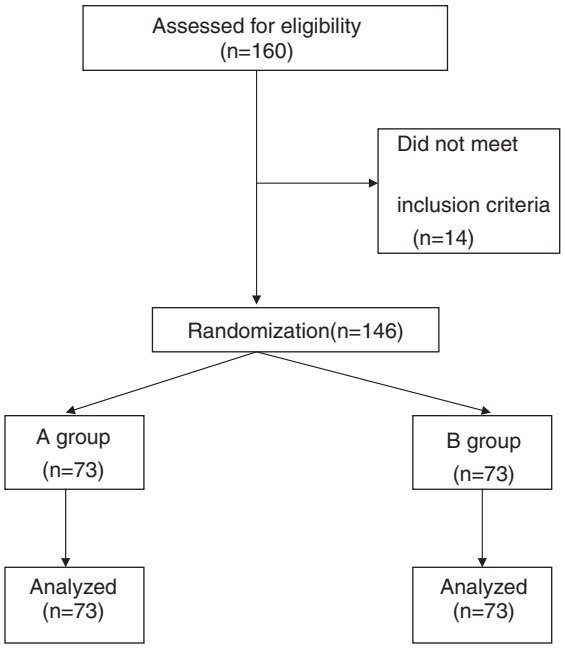

Figure 1 Flow diagram of progress through the phases of this study.

Microbiological efficacy

Sputum conversion rate (Table 4)

Sputum conversion rates were separated into two groups; group A (with SM, 73 cases) and group B (without SM, 73 cases). Subsequently, the rate of group A (71.2%) significantly improved compared with that for group B (50.7%). The sputum conversion rate revealed a significant difference between groups A and B in the two strains (*M. avium* and *M. intracellulare*), but no differences between the two strains. Regarding the existence of underlying respiratory diseases, there was a significant difference between patients with underlying respiratory diseases and those without underlying respiratory diseases in both groups. Sputum conversion rates were better in patients in group A without underlying respiratory diseases than those in group B without underlying respiratory diseases. They were also better in patients in group A with underlying respiratory diseases than those in group B with underlying respiratory diseases. As for extension of the lesion on radiological findings, there was a significant difference depending on the extension of the lesion in groups A and B. There was a significant difference in patients with extension of the lesion within one-third of the unilateral lung field between groups A and B, and there was also a significant difference in patients with extension of the lesion within the unilateral lung field between the two groups. There was also a significant difference in patients with extension of the lesion within bilateral lung fields. There were no significant differences in radiological characteristic findings such as bronchiectasis and cavity in groups A and B.

Table 2 Backgrounds of 146 cases with pulmonary MAC disease.

	A ($n = 73$)	B ($n = 73$)	*P*-value
Age (years)	63.8±10.6*	66.6±10.8	NS
Gender (male/female)	26:47	28:45	NS
Smoking habit (+)	30(41.1%)	33(45.2%)	NS
Chronic alcoholism	8(11.0%)	9(12.3%)	NS
Underlying disease	43(58.9%)	47(64.4%)	NS
Respiratory disease	27(37.0%)	29(39.7%)	NS
Non-respiratory disease	16(20.9%)	18(24.7%)	NS
Corticosteroid administration	3(4.1%)	4(5.5%)	NS
Previously healthy	30(41.1%)	26(35.6%)	NS
Prior antituberculous drugs before admission	16(21.9%)	14(19.2%)	NS

Table 3 Clinical findings of 146 cases with pulmonary MAC disease.

Clinical symptoms	A ($n = 73$)	B ($n = 73$)	*P*-value
Continuous cough	50(68.5%)	48(65.8%)	NS
Weight loss	12(16.4%)	13(17.8%)	NS
Hemosputum or hemoptysis	31(42.5%)	33(45.2%)	NS
Fever	20(27.4%)	18(24.7%)	NS
Microbiological findings			
Mycobacterium avium	38(52.1%)	36(49.3%)	NS
Mycobacterium intracellulare	35(47.9%)	37(50.7%)	NS
Radiological findings			
Extension of the lesion			
Within one-third of unilateral lung field	31(42.5%)	33(45.2%)	NS
Within unilateral lung field	34(46.5%)	32(43.8%)	NS
Over unilateral lung field	8(11.0%)	8(11.0%)	NS
Location of the lesion			
Right	14(19.2%)	16(21.9%)	NS
Left	8(10.9%)	7(9.6%)	NS
Bilateral	51(69.9%)	50(68.5%)	NS
Characteristic findings*			
Bronchiectasis	46(63.0%)	48(65.8%)	NS
Cavity	39(53.4%)	42(57.5%)	NS

*With repetition.

Sputum relapse rates (Fig. 2)
The sputum relapse rates were separated into two groups. There was no significant differences between group A (30.8%) and group B (35.1%), or in the sputum relapse rates in relation to the two strains of *M. avium* and *M. intracellulare*, the existence of underlying respiratory diseases, or extension of the lesion on radiological findings.

Clinical efficacy (Tables 5 and 6)

The overall outcome of both regimens was as follows: improved in 52 patients (35.6%), unchanged in 53 (36.3%), worsened in 37 (25.4%) and death in 4 (2.7%). The clinical improvement, when the two groups were considered separately (with and without SM), was better in group A than in group B with regard to the microbiological findings, underlying respiratory diseases and radiological findings, but there were no significant differences. There was no significant difference in clinical improvement between the two strains of *M. avium* and *M. intracellulare* in groups A and B. With regard to the existence of underlying respiratory diseases, there was no significant difference between patients with underlying respiratory diseases and those without them in the two groups. Finally,

Table 4 Sputum conversion rate for pulmonary MAC disease at the completion of treatment between group A and B.

	Group A ($n = 73$) (%)	Group B ($n = 73$) (%)	Total ($n = 146$) (%)
Microbiological findings			
Mycobacterium avium ($n = 74$)	71.1	47.2	59.5
Mycobacterium intracellulare ($n = 72$)	71.4	51.4	61.1
Underlying respiratory disease (+) ($n = 56$)	59.3	41.4	50.01
Underlying respiratory disease (−) ($n = 90$)	78.3	56.8	67.8
Radiological findings			
Extension of the lesion			
Within one-third of unilateral lung field	83.9	63.6	73.4
Within unilateral lung field	67.6	49.9	57.6
Bilateral lung field	37.5	12.5	25.0
Total	71.2	50.7	

$^{*}P<0.05$; $^{**}P<0.01$.

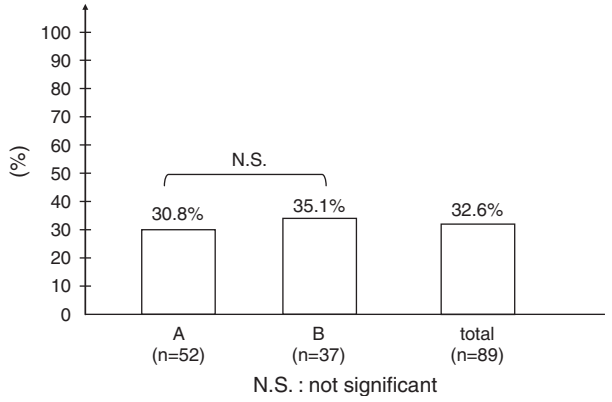

Figure 2 Sputum relapse rate for pulmonary MAC disease at the completion of treatment.

regarding extension of the lesion on radiological findings, there were no significant differences between the patients in the two groups having a lesion within one-third of the unilateral lung field, within the unilateral lung field, or within the bilateral lung field. There were also no significant differences in radiological characteristic findings such as bronchiectasis and cavity between the two groups.

Drug susceptibility test

A test of drug susceptibility to SM was performed on strains isolated from73 cases in group A. Among them, 38 strains (52%) were susceptible, 15 (21%) were intermediate, and 20 (27%) were resistant to SM. There were no significant differences in the sputum conversion rate of the patients infected with susceptible strains (28 of 38; 74%), intermediate strains (10 of 15; 67%), and resistant strains (14 of 20; 70%). The drug susceptibility to SM of patients who obtained clinical improvement (31 patients) who were susceptible was 18 of 31, 58%, intermediate 6 of 31, 19%, and resistant 7 of 31, 23%. The drug susceptibility to SM of patients who could not obtain clinical improvement (44 patients) who were susceptible was 20 of 44, 45%, intermediate 9 of 44, 20%, and resistant 15 of 41, 34%.

Adverse reactions

Adverse reactions, separated into the two groups, are shown in Table 7. In group A, adverse reactions appeared in 18 of 73 patients (24.7%) (including vertigo in three), while in group B, adverse reactions appeared in 15 of 73 patients (20.5%). However, there were no severe and irreversible adverse reactions or abnormal laboratory findings. There were no significant differences between the two groups with regard to the adverse reaction appearance rate and abnormal laboratory findings. The overall adverse reaction appearance rate was 22.6%.

Current status

The median duration of administration was 27.6 ± 7.8 months (24–36 months) in group A and 28.4 ± 8.0 months (24–42 months) in group B. The median duration of follow-up was 15.6 ± 4.8 months (12–36 months) in group A and 16.4 ± 5.0 months (12–36 months) in group B.

The mortality rates of both groups were comparatively good, 2.7% for group A and 2.7% for group B. The causes of death were advanced pulmonary MAC disease in one and complicating bacterial pneumonia in 1 patient in both groups A and B. All of the patients who died in both groups were elderly and had a past history of healed pulmonary tuberculosis.

Table 5 Pulmonary MAC disease outcome.

	A ($n = 73$)	B ($n = 73$)	Total ($n = 146$)
Improving	31 (42.5%)	21 (28.8%)	52 (35.6%)
Unchanging	25 (34.2%)	28 (38.4%)	53 (36.3%)
Worsening	15 (20.6%)	22 (30.1%)	37 (25.4%)
Death	2 (2.7%)	2 (2.7%)	4 (2.7%)

The clinical course of 31 patients (42.5%) in group A which showed clinical improvement worsened in 15 (48.4%) within 1 year after the completion of treatment. The time between sputum conversion and relapse was 3.6 ± 1.2 months in group A. The treatment of these patients thereafter was as follows: the same treatment in 9 patients, new quinolone (levofloxacin) administration in four, and surgical operation in two. Five of the 15 patients responded to the salvage regimen and obtained clinical improvement. The clinical course of 21 patients (28.8%) in group B who had clinical improvement worsened in 11 (52.4%) within 1 year after the completion of treatment. The time between sputum conversion and relapse was 3.2 ± 1.2 months. The treatment of these patients was as follows: treatment including SM in 8 patients, new quinolone administration in two,

Table 6 Clinical improvements for pulmonary MAC disease at the completion of treatment between group A and B.

	Group A ($n = 73$) (%)	Group B ($n = 73$) (%)	Total ($n = 146$) (%)
Microbiological findings			
Mycobacterium avium ($n = 74$)	42.1	27.8	35.1
Mycobacterium intracellulare ($n = 72$)	42.9	29.7	36.1
Underlying respiratory disease (+) ($n = 56$)	33.3	20.7	26.8
Underlying respiratory disease (−) ($n = 90$)	47.8	34.1	41.1
Radiological findings			
Extension of the lesion			
Within one-third of unilateral lung field	51.6	36.4	43.8
Within unilateral lung field	41.2	28.3	34.8
Bilateral lung field	17.5	0	6.3
Total	42.5	28.8	35.6

Table 7 Adverse reactions and abnormal laboratory findings.

A ($n = 73$)		B ($n = 73$)		Total ($n = 146$)	
Adverse reactions					
18(24.7%)		15(20.5%)		33(22.6%)	9
Appearance rate items					
Liver dysfunction	4	Liver dysfunction	5	Liver dysfunction	
Vertigo	3	Gastrointestinal symptom	4	Gastrointestinal symptom	7
Gastrointestinal symptom	3	Visual disturbance	3	Visual disturbance	5
Visual disturbance	2	Eruption	2	Eruption	4
Eruption	2	Fever	1	Vertigo	3
Fever	2			Fever	3
Eruption+gastrointestinal	1			Eruption+gastrointestinal	1
Symptom				Symptom	
Fever+liver dysfunction	1			Fever+liver dysfunction	1

and surgical operation in one. Four of 11 patients responded to the salvage regimen and obtained clinical improvement.

Discussion

Nontuberculous mycobacterial diseases have been divided into two groups due to the response to treatment using antituberculous drugs: one consists of diseases caused by *M. kansasii* and *M. szulgai*, which show clinical characteristics resembling *M. tuberculosis* which has shown a good response to treatment using antituberculous drugs. The other consists of ones caused by MAC and *M. fortuitum*, which show clinical characteristics resembling nontuberculous mycobacteria, which have shown no response to treatment using antituberculous drugs. The treatment of pulmonary MAC disease was at first difficult because there were no antibiotics available having a complete bactericidal effect with the usual dosage, there was no definite standard drug sensitivity examination in vitro, and there was no parallel between the results of drug sensitivity examinations in vitro and the clinical effect in vivo. Although the ATS proposed original guidelines concerning the treatment for nontuberculous mycobacterial diseases in 1990, it emphasized that it was not useful to employ the drug sensitivity examination convienient for tuberculosis for the treatment of nontuberculous mycobacterial diseases except to check RFP sensitivity for *M. kansasii*.[6] For these reasons, the treatment of pulmonary MAC disease has largely depended on the experience of respiratory specialists in isolating the causative microorganisms, not on the results of drug sensitivity examinations. The ATS finally recommended combined therapy using RBT or RFP, EB, CAM or azithromycin (AZM) and SM as the treatment guidelines for pulmonary MAC disease in 1997.[4] Among these guidelines, SM was recommended for use for extensive pulmonary MAC disease intermittently (two or three times per week) for the first 2–3 months of therapy. The exact dose of SM in the recommended multidrug regimen may depend on the patient's age and weight (0.75–1.0 g per once). We decided on a dose of SM of 15 mg/kg three times per week because there were no patients with renal dysfunction in group A. However, although SM was employed three times per week at a dose of 15 mg/kg in this study, we had to carry out dose finding prospective study of SM afterwards to decide appropriate daily dose or frequency of SM. We also had to perform a double-blind comparative study using other drugs such as new quinolone with SM to confirm the clinical efficacy for pulmonary MAC disease compared with that of other drugs. No previous reports have compared CAM-containing regimens with and without an aminoglycoside. Therefore, we performed the first prospective double-blind randomized trial to make sure of the utility of SM for the treatment of pulmonary MAC disease.

Subsequently, although there were no significant differences in the patients' backgrounds and the severity of pulmonary MAC disease in either group, the sputum conversion rate in group A (with SM) was significantly higher than that in group B (without SM), as shown in Table 4. As for the sputum relapse rate and clinical improvement, although there were no significant differences between the groups, group A showed better results than group B, as shown in Fig. 2 and Tables 5 and 6. The higher clinical efficacy observed with the addition of SM may not be related to the MIC of SM in vitro. In this study, there were cases with a low MIC of SM in which efficacy was not high and there were also cases with a good response in spite of a high MIC of SM in group A. Wallace et al. reported a good relationship between microbiological or clinical efficacy and the drug sensitivity test with CAM alone,[3,7,8] Iseman reported [9] that in vitro susceptibility testing and therapeutic drug monitoring of other antituberculous drugs containing CAM is also useful to optimize efficacy and reduce toxicity. These results suggest both the possibility of additive or synergistic effects with other drugs due to SM or of partial effects for polyclonal MAC infections. It is assumed that all patients had macrolide antibiotics (CAM or AZM) susceptible MAC isolates because there were no patients who were previously treated with macrolide antibiotics.(Fig. 3)

Regarding side effects, such as ototoxicity or renal toxicity due to SM, irreversible problems were fortunately not detected in any patients in either

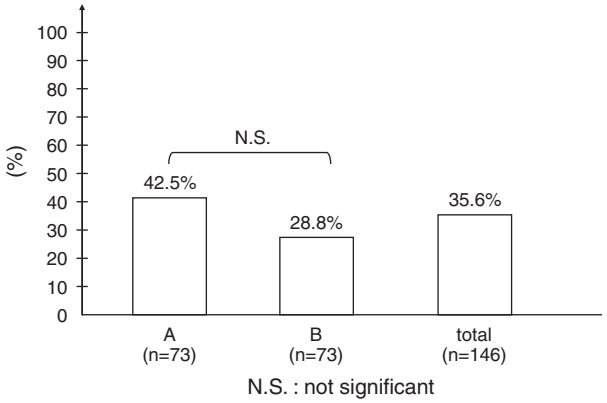

Figure 3 Clinical improvement for pulmonary MAC diseases at the completion of treatment.

group. Vertigo appeared in 3 patients (4%) in group A, but it was not severe and the administration of SM has been continued. However, because ototoxicity due to SM is often irreversible, patients receiving SM should be instructed about the signs and symptoms of toxicity (unsteady gait, tinnitus, diminished hearing) at the start of therapy and again on subsequent visits, with discontinuation or decrease in dosage or frequency if suggestive signs of toxicity occur. There were no significant differences in the appearance rate or items between the groups, as shown in Table 7.

Finally, because the method of assessment was restricted to the sputum conversion rate of MAC strains before and after treatment in previous reports,[2,10] we believe it is difficult to grasp the clinical efficacy of the treatment on patients according to the ATS guidelines from the assessments made in other reports. Therefore, we carried out assessment of clinical improvement based on the clinical symptoms and/or the extent of lesions on chest roentogenograms and chest CT instead of including the subjective assessments of several respiratory specialists.

In conclusion, we support treatment including SM according to both guidelines (ATS and JST) for patients with pulmonary MAC disease without HIV infection based on the findings of this randomized study because there were no irreversible major side effects due to SM. However, as we have not been able as yet to clarify the mechanism, which makes SM effective against MAC strains, further studies are required.

References

1. Sakatani M. Nontuberculous mycobacteriosis (NTM) in Japan—epidemiologic and clinical study. *Kekkaku* 1994;**69**: 119–24.
2. Wallace RJ, Brown BA, Griffith DE, Girard WM, Murphy DT, Wallace Jr RJ. Clarithromycin regimens for pulmonary *Mycobacterium avium* complex: the first 50 patients. *Am J Crit Care Med* 1996;**153**:1766–72.
3. American Thoracic Society. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. *Am J Respir Crit Care Med* 1997;**156**:S1–S25.
4. Opinions of Japanese Society for Tuberculosis committee on therapy of atypical mycobacterium infections. *Kekkaku* 1998;**73**:599–605.
5. Wallace Jr. RJ, Nash DR, Steele LC, Steingrube V. Susceptibility testing of slowly growing mycobacteria by a microdilution MIC method with 7H9 broth. *J Clin Microbiol* 1986;**24**:976–81.
6. American Thoracic Society. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. *Am Rev Respir Dis* 1990;**142**:940–54.
7. Wallace RJ, Brown BA, Griffith DE, et al. Initial clarithromycin monotherapy for *Mycobacterium avium–intracellulare* complex lung disease. *Am J Respir Crit Care Med* 1994; **149**:1335–41.
8. Dautzenberg B, Piperno D, Diot P, Trufot-Pernot C, Chauvin JP. Clarithromycin Study Group of France. Clarithromycin in the treatment of *Mycobacterium avium* patients without AIDS. *Chest* 1995;**107**:1035–40.
9. Iseman MD. Medical management of pulmonary diseases caused by *Mycobacterium avium* complex. *Clin Chest Med* 2003;**23**:635–41.
10. Tanaka E, Kimoto T, Tsuyuguchi K, et al. Effect of clarithromycin regimen for *Mycobactrerium avium* complex pulmonary disease. *Am J Respir Crit Care Med* 1999;**160**: 866–72.